REMARKS

Claims 1 – 19 are now pending in the application. Claim 8 is withdrawn from consideration, as being directed to a non-elected invention. If claims 1-19 are allowed, the applicants request that the Examiner contact the undersigned to assist the Examiner in preparing an Examiner's amendment to allow for the rejoinder of the subject matter of claim 8. No new matter has been added.

Applicants respectfully requests allowance of the pending claims in light of the amendments made herein.

Claim Objections

Applicants have amended the pending claims to remove non-elected subject matter as requested by the Examiner to overcome the claim objections.

Claim Rejections – 35 U.S.C. § 101

Claim 10 was rejected under 35 U.S.C. § 101 as allegedly failing to set forth any steps involved in the recited use. The use claims have been converted into method of use claims in order to comply with U.S. practice.

Claim Rejections – 35 U.S.C. § 112

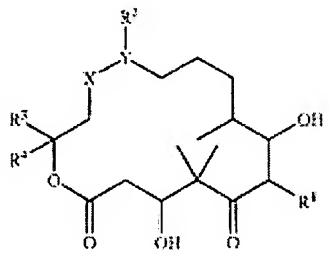
Claim 10 was rejected for allegedly failing to be enabling for treating all cancers, as an unpredictable art, while at the same time acknowledging that the specification was enabling for treating some cancers. It is respectfully presented that the scope of enablement must only bear a "reasonable correction" to the scope of the claims, and the Specification does not need to provide working models for all indicated uses. Applicants have provided general enablement for the use of novel epothilones for the treatment of various types of cancer by its references on page 1 of the Specification to Nicolau et al. in Angew. Chem. Int. Ed. 1998, 37, 2014-45 and Flörsheimer et al. in Exert. Opin. Ther. Patents, 2001, 11, 951-69. Applicants wish to note that these references support the general proposition that epothilone-type derivatives have anticancer properties similar to other anticancer drugs, such as paclitaxel, based on their action as mitosis inhibitors, microtubule-modifying agents, and cytotoxic agents or fungicides. Without being

limited to the following, the references further indicate that cancers that appear responsive to treatment by specific epothilone molecules include multi-drug-resistant cancers, solid cancer tumors, leukemia (cancer of the blood or bone marrow), and cancers of the breast, ovaries, prostate, lung, and colon. As additional support, Applicants have included copies of several epothilones that are currently the subject of clinical investigations as listed in the U.S. National Institutes of Health, National Cancer Institute database for the following cancers: ovarian, fallopian, lung, peritoneal, colorectal, prostate, breast, solid tumors, advanced malignancies, and breast cancer with brain metastases. As such, there has been no evidence presented in the office action which contradicts that the epothilone-class of compounds would be expected to have anti-cancer activity.

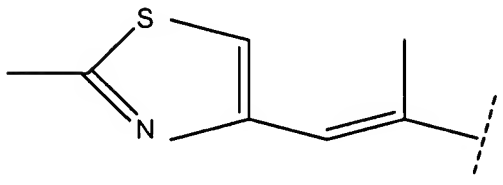
Applicants have added new claims to reflect the uses to treat some of these specific forms of cancer.

Claim Rejections – 35 U.S.C. § 102

Claims 1-4, 6-7, and 9-10 were rejected under 35 U.S.C. § 102 as allegedly being anticipated by Vite et al. (WO 99/02514A2, or "WO '514"). This rejection requires in the present invention R^1, R^2, R^3 to be methyl for the compound



X-Y to be an epoxide, and R^4 to be



Applicants respectfully asserts that claims 1-2 WO '514 concern a very general chemical compound formula as a genus, whereas the presently amended claims, for example claim 3, provide a more specific genus or specific compound that is novel. Anticipation cannot be

established simply by presenting an ad hoc collection of elements, i.e., in order to establish anticipation, "[t]he identical invention must be shown in as complete detail as is contained in the...claim." *See* MPEP 2131 and *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Vite clearly fails this standard for anticipation even for Applicants' claim 1 and is also fails for the narrower embodiments of the claimed compounds (i.e., claims 2-7).

Claim Rejections – 35 U.S.C. § 103

Claims 1-7 and 9-10 were rejected as allegedly obvious over WO '514 in view of Patani et al. (*Chemical Reviews*, 1996, 3147-3176).

It was acknowledged that WO '514 does not teach a trifluromethyl group in place of a methyl group at the R^3 position, for which Patani is allegedly cited at 3149-50 for the authors' discussion for substituting fluorine for hydrogen to "yield new pharmaceuticals with similar utility and comparable, if not increase [sic]m activity." Office Action (March 5, 2007) at 11. Applicants asserts that the prima facie case of obviousness was improperly maintained for combining these teachings, i.e. while it is predictable that the class of epothilones act as anticancer agents, and are enabled, this does not teach or suggest the making or using of the new and specific epothilone derivative compounds claimed by the applicants. In addition, it cannot even be argued that it would have been "obvious to try" making the applicants' claimed compound because Patani teaches away from making the applicants' claimed substitution by stating that fluorine substitutions may result in derivatives that can alter enzymatic processes or other biological reactions. Patani at 3149.

Applicants have amended claim 10 and included new claim 11 to reflect that the novel and unobvious compounds may be used as cytotoxic agents for the treatment of cancer.

Claims 1-4, 6-7, and 9 were also rejected as allegedly obvious over Hoefle (U.S. Patent No. 6,288,237, Col. 14, lines 15-38).

Applicants assert that these references are overcome for the reasons as cited above, even following the Examiner's assumptions of various constituent substitutions, where Hoefle does not teach the R^3 group can be methyl. Applicants respectfully assert, moreover, that the Examiner has failed to demonstrate a prima facie case that the additional methyl substitution would be obvious in light of the stearic effects introduced by a bulky methyl group over a

hydrogen, and Hoefle further includes no motivation to substitute the methyl group for the other listed substituents.

The Applicants also note that Claim 1 of the '237 patent differs from the Applicants' invention in a least two ways.

First, in the presently claimed invention, the variable R^3 and R^4 are not hydrogen; in the corresponding position for the compound of claim 1 in the '237 patent, there is a hydrogen atom attached to the carbon.

Second, the variable R^2 in claim 1 of the '237 patent fixes the moiety at that position to be -OH or some other derivative thereof. The corresponding position of the presently claimed compound is clearly a -C(=O)-.

There is no basis from within the '237 reference or from the art in general which would have directed one of ordinary skill in the art to make the requisite substitutions promulgated in the Office Action especially when considering the person of ordinary skill in the art would not have the benefit of the Applicants' claim before them to act as a roadmap as does the Examiner for examination purposes.

Therefore, the claims are not obvious over the '237 patent.

Provisional Double Patenting

Claims 1-4, 6-7, and 9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,288,237. The Applicants request reconsideration of this provisional rejection in that consideration of obviousness double patenting, unlike consideration for obviousness under 103(a), is except for rare circumstances, limited to the comparison of the respective claims. However, Claim 1 of the '237 patent differs from the Applicants' invention in a least two ways.

First, in the presently claimed invention, the variable R^3 and R^4 are not hydrogen; in the corresponding position for the compound of claim 1 in the '237 patent, there is a hydrogen atom attached to the carbon.

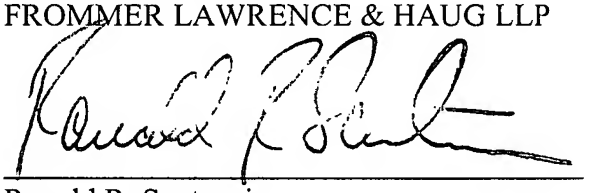
Second, the variable R^2 in claim 1 of the '237 patent fixes the moiety at that position to be -OH or some other derivative thereof. The corresponding position of the presently claimed compound is clearly a -C(=O)-.

When limited to strictly a comparison of the claims, there is no basis to make the requisite substitutions and therefore the claims should not be rejected on obviousness-type double patenting grounds.

CONCLUSION

Reconsideration and withdrawal, or modification of the restriction requirement, and allowance of the presently amended claims, is respectfully requested.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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NCI Drug Dictionary

epothilone B
A compound isolated from the myxobacterium Sorangium cellulosum. Similar to paclitaxel, epothilone B induces microtubule polymerization and stabilizes microtubules against depolymerization conditions. In addition to promoting tubulin polymerization and stabilization of microtubules, this agent is cytotoxic for cells overexpressing P-glycoprotein, a characteristic that distinguishes it from the taxanes. Epothilone B may cause complete cell-cycle arrest. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus)

Synonyms:	(-)-Epothilone B patupilone
Code name:	EPO906
Chemical structure name:	(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Previous: epirubicin hydrochloride, Epitol, epoetin alfa, epoetin beta, Epogen
Next: epothilone D, epothilone ZK-219477, epratuzumab, erb-38 immunotoxin, Erbitux

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Search Criteria

Protocol Search ID:	3516588
Type of Cancer:	All
Type of Trial:	All
Status of Trial:	active trials
Drug:	epothilone B
Drug Combination Search:	No
Phase of Trial:	All
Sponsor of Trial:	All
Special Category:	All

1. Patupilone vs Pegylated Liposomal Doxorubicin in Taxane/Platinum Refractory/Resistant Patients With Recurrent Epithelial Ovarian, Primary Fallopian or Primary Peritoneal Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase III	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2303** NCT00262990

2. EPO906 in Patients With Late Stage Non-Small-Cell Lung Cancer (NSCLC)

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II, Phase I	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A 2209** NCT00088127

3. Phase I/II Study of Celebrex and EPO906 in Patients With Metastatic Colorectal Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II, Phase I	Treatment	Active	18 and over	Other	**3c-03-19** NCT00159484

4. Study of Patupilone in Patients With Brain Metastasis From Non-Small Cell Lung Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2227** NCT00219297

5. EPO906 Therapy in Patients With Advanced Ovarian, Primary Fallopian, or Primary Peritoneal Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 to 85	Pharmaceutical / Industry	**CEPO906A2203** NCT00035100

6. Study of Patupilone in Prostate Cancer Patients Who Progress After Hormone Therapy and Docetaxel Chemotherapy

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Other	**OZM-005/CEPO906A2402** NCT00407251, OZM-005, Protocol number CEP0906A2402

7. Efficacy and Safety of Patupilone in Men (=18 Years) With Metastatic Hormone Refractory Prostate Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2229** NCT00411528

Last Modified: 6/27/2007 **First Published:** 3/16/2007

8. Phase II Study of Epothilone B in Patients With CNS Metastases Secondary to Breast Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	NCI	**CASE-5106** CASE-IRB-5106-CC185, MSKCC-07036, NCT00450866, CASE 5106

9. EPO906 Plus Radiation Therapy for the Treatment of Cancer Patients

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Treatment	Active	18 and over	Other	**03C.275** NCT00328458

10. Efficacy and Safety of Patupilone in Patients With Advanced Solid Tumors in Japan

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Treatment	Active	20 and over	Pharmaceutical / Industry	**CEPO906A1103** NCT00412789

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Search Criteria

Protocol Search ID:	3516588
Type of Cancer:	All
Type of Trial:	All
Status of Trial:	active trials
Drug:	epothilone B
Drug Combination Search:	No
Phase of Trial:	All
Sponsor of Trial:	All
Special Category:	All

1. A Study of Patupilone in Patients With Advanced Solid Tumors and Varying Degrees of Hepatic Function

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Biomarker/Laboratory analysis, Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2121** NCT00420524

2. Evaluate the Effects of Patupilone on the Pharmacokinetics of Midazolam and Omeprazole in Patients With Advanced Malignancies

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Biomarker/Laboratory analysis, Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2123** NCT00420615

3. A Study of Patupilone in Patients With Advanced Solid Tumors and Varying Degrees of Hepatic Function

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO9062121E1** NCT00421044

4. Combination Trial of Patupilone and Carboplatin in Adult Patients With Advanced Solid Tumors

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2105** NCT00426582

5. Evaluate the Effects of Patupilone on the Pharmacokinetics and Pharmacodynamics of Warfarin in Patients With Advanced Malignancies

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Biomarker/Laboratory analysis, Treatment	Active	18 and over	Pharmaceutical / Industry	**CEPO906A2120** NCT00448396

6. Phase I Study of Patupilone and RAD001

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Treatment	Active	18 and over	Other	**050612-0220060307** NCT00496600, CRAD001US16

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NCI Drug Dictionary

epothilone D
A natural polyketide compound isolated from the myxobacterium Sorangium cellulosum. Also known as desoxyepothilone B, epothilone D binds to tubulin and inhibits the disassembly of microtubules, resulting in the inhibition of mitosis, cellular proliferation, and cell motility. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus)

Synonyms:	12,13-Deoxyepothilone B desoxyepothilone B
Code name:	KOS 862
Chemical structure name:	(4S-(4R*,7S,8R*,9R*,13Z,16R*(E)))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl) oxacyclohexadec-13-ene-2,6-dione

Previous: Epitol, epoetin alfa, epoetin beta, Epogen, epothilone B
Next: epothilone ZK-219477, epratuzumab, erb-38 immunotoxin, Erbitux, erlotinib hydrochloride

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NCI Drug Dictionary

epothilone ZK-219477
A novel synthetic epothilone with potential antineoplastic activity. Epothilone ZK-219477 binds to microtubules, predominantly in tumor cells, thereby inducing microtubule bundling, formation of multipolar spindles, and mitotic arrest in a manner similar to taxanes. Epothilones are poor substrates for the multidrug resistance 1 (MDR1) P-glycoprotein drug efflux pump and, unlike the taxanes, appear to be able to evade some drug-resistance mechanisms. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus)

Synonym:	ZK-Epothilone
Code names:	SHY03757 ZK-219477

Previous: epoetin alfa, epoetin beta, Epogen, epothilone B, epothilone D
Next: epratuzumab, erb-38 immunotoxin, Erbitux, erlotinib hydrochloride, ertumaxomab

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Search Criteria

Protocol Search ID:	3516605
Type of Cancer:	All
Type of Trial:	All
Status of Trial:	active trials
Drug:	epothilone ZK-219477
Drug Combination Search:	No
Phase of Trial:	All
Sponsor of Trial:	All
Special Category:	All

1. ZK-Epo Given With Carboplatin in Patients With Recurrent Ovarian Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II, Phase I	Treatment	Active	18 and over	Pharmaceutical / Industry	**307979** NCT00325351

2. A Study of a New Chemotherapy Agent in Combination With Cisplatin to Treat Small Cell Lung Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II, Phase I	Treatment	Active	18 and over	Pharmaceutical / Industry	**310101** NCT00359359, EudraCT No: 2006-000067-29

3. Safety and Efficacy Study of a New Chemotherapy Agent to Treat Non-Small-Cell Lung Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**307971** NCT00160069

4. Safety and Efficacy Study of a New Chemotherapy Agent to Treat Metastatic Breast Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**309544** NCT00288249, EudraCT No: 2005-003216-30

5. Evaluation of a New Agent for Treatment of Advanced Stage Breast Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**307975** NCT00313248

6. ZK-Epo Given With Prednisone in Patients With Metastatic Androgen-Independent Prostate Cancer

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs

Phase II	Treatment	Active	18 and over	Pharmaceutical / Industry	**307976** NCT00350051

7. Epothilone in Recurrent Glioblastoma Patients

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 to 70	Other	**ZK219477IV** NCT00397072

Last Modified: 7/19/2007 **First Published:** 1/5/2007

8. Phase II Study of Epothilone ZK-219477 in Patients With Recurrent Glioblastoma

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Biomarker/Laboratory analysis, Treatment	Active	18 and over	Other, Pharmaceutical / Industry	**EORTC-26061** EUDRACT-2006-001659-37, SPRI-EORTC-26061, NCT00424060

9. ZK219477 in Patients With Breast Cancer and Brain Metastases

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Other	**06-268** NCT00496379

10. Investigation Into How the Body Takes up the Test Drug and Distributes it Into Various Body Organs and Tissues, How it Processes the Drug and How it Ultimately Removes it

Phase	Type	Status	Age Range (yrs)	Sponsor	Protocol IDs
Phase I	Biomarker/Laboratory analysis, Treatment	Active	18 and over	Pharmaceutical / Industry	**310301** NCT00432302, EUDRA-CT 2006-000188-26